

**MAGNITUDE AND DURATION OF THE EFFECTS
OF COCAINE ON CONDITIONED AND ADJUNCTIVE
BEHAVIORS IN THE CHIMPANZEE**

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Characteristic patterns of conditioned key-pressing were maintained in the chimpanzee under a multiple 30-response fixed-ratio, 10-minute fixed-interval schedule of food presentation. Adjunctive drinking occurred with regularity during the fixed-interval schedule and, with less frequency, during 1-minute timeout periods that followed each food presentation; drinking seldom occurred during the fixed-ratio schedule. Cocaine increased key pressing under the fixed-interval schedule at doses between .1 and 3.0 mg/kg, but adjunctive drinking and key pressing under the fixed-ratio schedule did not increase at any dose. Conditioned and adjunctive behaviors were disrupted and suppressed for different durations at 10.0 mg/kg, a dose which induced convulsive seizures within 10 minutes after intramuscular injection. A time-course analysis showed the magnitude and duration of the effects of cocaine on key pressing under the fixed-interval schedule and on adjunctive drinking to be dose-related. Moreover, a given dose of cocaine had diverse effects, depending on the behavior and the time since drug administration.

Key words: conditioned behavior, adjunctive behavior, multiple FR FI schedules, cocaine, chimpanzees

Cocaine is a psychoactive substance that enjoys both legitimate clinical use as a local anesthetic and illicit use as a recreational drug. It has excitatory effects on spontaneous electroencephalographic (EEG) activity (Matsuzaki, 1976; Wallach & Gershon, 1971), blocks uptake of catecholamines (Chiueh & Kopin, 1978; Trendelenburg, 1959), alters cardiovascular activity by increasing blood pressure and heart rate (Fischman, Schuster, Resnekov, Shick, Krasnegor, Fennell, & Freedman, 1976; Gonzalez & Byrd, 1977; Resnick, Kestenbaum, & Schwartz, 1977), increases respiratory rate (Ritchie, Cohen, & Dripps, 1970) and body temperature (Gonzalez & Byrd, 1977), and stimulates psychomotor behavior (Ellinwood & Kilbey, 1977; Jaffe, 1975; Woods & Downs, 1973). The effects of cocaine on the central nervous system (CNS) can be extensive; consequently, the effects on behaviors mediated by the CNS have been a subject of considerable

interest and importance. Behavioral experiments have shown that cocaine increases spontaneous motor activity in mice (Dews, 1953; Smith, 1965) and can reinforce and maintain key pressing in rats (Pickens & Thompson, 1968) and monkeys (Kelleher, 1976) when intravenous cocaine injection is response dependent. When cocaine is administered as pre-treatment before a behavioral session, the drug enhances responding and increases response rate maintained under fixed-interval schedules in pigeons (Smith, 1964) and monkeys (Barrett, 1976; Byrd, 1979; Gonzalez & Goldberg, 1977; Spealman, Goldberg, Kelleher, Goldberg, & Charlton, 1977). However, cocaine typically decreases responding under fixed-ratio schedules in rats (MacPhail & Seiden, 1975), pigeons (Smith, 1964) and monkeys (Gonzalez & Goldberg, 1977; Spealman et al., 1977).

In contrast to the data describing the effects on schedule-controlled behavior, the effects of cocaine on adjunctive or intercurrent behaviors are less well documented. The present report describes the effects of cocaine on two types of behavior, conditioned and adjunctive, in the chimpanzee and the time-course of the effects of cocaine on these behaviors. Conditioned key pressing was maintained under a multiple schedule of food presentation com-

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prising fixed-interval and fixed-ratio components, and adjunctive drinking occurred in concert with the component schedules. Cocaine administered before a daily session increased responding during the fixed-interval components at doses that (a) decreased drinking and (b) had no effect on responding during the fixed-ratio components.

METHOD

Subjects

Two male chimpanzees (*Pan troglodytes*), 9 to 12 years of age, were housed individually and maintained at approximately 85% of their free-feeding weights (18 and 22 kg) by regulating daily food rations. Water was continuously available. Each chimpanzee had extensive experience under various schedules of food presentation and each was trained to accept intramuscular injections as described previously (Byrd, 1975, 1977).

Apparatus

Experimental observations and data collection were made while each chimpanzee was in a metal cage within a ventilated sound-attenuating chamber (Industrial Acoustic Company, Model AC-5). One wall of the cage supported a response key (cf. Byrd, 1974), a food tray, a water tube, and a 4.0 cm by 5.0 cm translucent Plexiglas panel that could be transilluminated by 7.5-W bulbs. A downward force of approximately 100 g (1.0 N) on the response key produced an audible click of a relay and operated switching circuitry. Reinforcement of key pressing comprised the operation of a Universal Feeder (R. Gerbrands Company, Model 70) and the consequent delivery of two Purina monkey biscuits (approximately 7 g) into the food tray. Lip pressure on the water tube operated a solenoid and related electrical circuitry and released 5.0 ml of tap water. A 25-W houselight in the ceiling of the chamber was continuously illuminated during the session, and white noise masked extraneous sounds. Switching circuitry controlled conditions in the chamber and recorded data.

Procedure

Before the daily 2-hr session in the experimental chamber, the chimpanzee extended its right arm through an opening in one wall of

the living area and on designated days received an intramuscular injection of either saline or drug solution. The chimpanzee was then placed promptly in the experimental chamber. The daily session in the chamber began less than 5 min postinjection with a 15-min timeout period during which the panel lights were darkened, responses (key presses) had no consequences, and water was available via the water tube. On termination of the timeout, the red panel light was illuminated and responding was reinforced according to a fixed-ratio (FR) schedule, i.e., the 30th response in the presence of the red light resulted in food presentation (FR 30). After a 1-min timeout, the white panel light was illuminated and responding was reinforced according to a fixed-interval (FI) schedule, i.e., the first response to occur after 10 min had elapsed in the presence of the white light resulted in food presentation (FI 10 min). The FR 30 and FI 10-min schedules alternated during the session (*mult FR FI*), with each occurring nine times and each followed by a 1-min timeout. If the FR schedule was not completed within 30 sec or if the FI schedule was not completed within 630 sec, the panel lights were darkened, food was not presented, and a 1-min timeout ensued. Whenever the feeder operated, the food tray was illuminated with white light. Tap water was continuously available in the experimental chamber, and its delivery was independent of key pressing.

Before receiving the first administration of cocaine, each chimpanzee had been exposed to the multiple schedule for a minimum of 12 months. As a result, there were no systematic changes in any mean values characterizing performance during periods of 5 to 6 successive daily sessions. Cocaine hydrochloride was dissolved in distilled water for injection, and doses (.01 to 10.0 mg/kg) were determined in terms of the salt. Sodium chloride solution (.9%) was substituted for cocaine on five occasions and served as control (placebo) injections. All injections were in a volume of .5 to 1.0 ml and were given no more frequently than twice a week. The three smaller doses were studied twice in each chimpanzee and the two larger doses only once. The sequence of dose administration was .1, 1.0, 3.0, .3, .3, .1, 10.0, and 1.0 mg/kg for chimpanzee C-1 and .1, 1.0, 3.0, .3, 1.0, .3, 10.0, and .1 mg/kg for chimpanzee C-6.

RESULTS

Control Data

Rates and patterns of key pressing during sessions without cocaine were similar to performances typically maintained under *mult* FR FI schedules in various animal subjects (Byrd, 1973, 1975; Clark & Steele, 1966; Ferster & Skinner, 1957; Kelleher & Morse, 1964; Waller, 1961). Responding under the FR 30 schedule comprised a pause (period of no responding) following illumination of the red light, then the initiation of a relatively high, steady rate of responding that persisted until food presentation. Mean response rates under the FR 30 schedule and the mean pause time between onset of the red light and occurrence of the first response during control (saline) sessions are shown in Table 1. Responding under the FI 10-min schedule comprised a period of little or no responding following illumination of the white light, then a gradual increase in responding during the remainder of the 10-min interval. Performance under the FI schedule was quantified in terms of mean response rate and the patterning or distribution of responses during the 10-min interval. The latter was expressed as a quarter-life percentage as described by Gollub (1964) and Herrnstein and Morse (1957). If responses were distributed uniformly throughout the interval, quarter life

would be 25%; a quarter life greater than 25% indicated that a relatively greater number of responses occurred during the last segments of the interval. Table 1 shows control (saline) rates and quarter-life values for the FI 10-min schedule. Responding typically did not occur during timeout periods.

Water intake during the experimental session occurred in concert with phases of the *mult* FR FI schedule of key pressing. Water intake was highest during the FI schedule, was lower during timeout periods, and seldom occurred during the FR schedule. The greatest amount of drinking typically occurred during the first half of the 10-min FI when rates of key pressing were low. Characteristic amounts of water ingested per session for each chimpanzee are shown in Table 1.

Drug Effects

Cocaine increased mean rates of responding under the FI schedule at doses that decreased adjunctive drinking and had no effect on rates under the FR schedule. There was little effect on overall mean rate of responding under the FI schedule at .1 mg/kg, but at .3 and 1.0 mg/kg responding increased substantially, with the average response rate in chimpanzee C-1 increasing to more than twice the rate observed in the absence of the drug. Increasing the dose to 3.0 mg/kg did not result in higher

Table 1

Behavioral measures. The saline values are means (± 1 S.D.) of five sessions under multiple FR 30 FI 10 min. The drug data are mean values after two (for .1, .3, and 1.0 mg/kg) or one (for 3.0 and 10.0 mg/kg) administrations of cocaine. Water intake is total amount per session; all other data are mean values per component.

Subject & dosage	FI rate (responses/sec)	Quarter-life (%)	FR rate (responses/sec)	FR pause time (sec)	Water intake (ml)
<i>C-1</i>					
Saline	.034 ($\pm .009$)	81.3 (± 5.5)	1.36 ($\pm .19$)	104.2 (± 21.0)	2218 (± 350)
.1 mg/kg	.032	74.4	1.45	92.3	1973
.3 mg/kg	.045	68.7	1.38	94.8	2198
1.0 mg/kg	.070	66.3	1.45	98.7	1923
3.0 mg/kg	.067	57.0	1.63	85.1	1160
10.0 mg/kg	.000	—	1.33	128.5	0
<i>C-6</i>					
Saline	.388 ($\pm .034$)	37.4 (± 3.4)	2.33 ($\pm .21$)	21.1 (± 8.5)	410 (± 132)
.1 mg/kg	.370	38.2	2.48	19.8	320
.3 mg/kg	.630	34.2	2.54	15.7	418
1.0 mg/kg	.580	31.2	2.59	15.8	343
3.0 mg/kg	.110	14.9	2.63	13.5	30
10.0 mg/kg	.110	12.6	1.05	121.6	40

mean rates of responding in either chimpanzee, and responding was markedly suppressed at 10.0 mg/kg. Figure 1 (top) shows mean response rates under the FI schedule as a percentage of the rates under control (saline) conditions for the two chimpanzees. Analyzing and plotting the FI response rates and other behavioral measures in this manner revealed more clearly the similarity of the dose-effect functions in the two chimpanzees despite differences between them in the absolute values of the measures (see Table 1).

In addition to changes in response rate, the

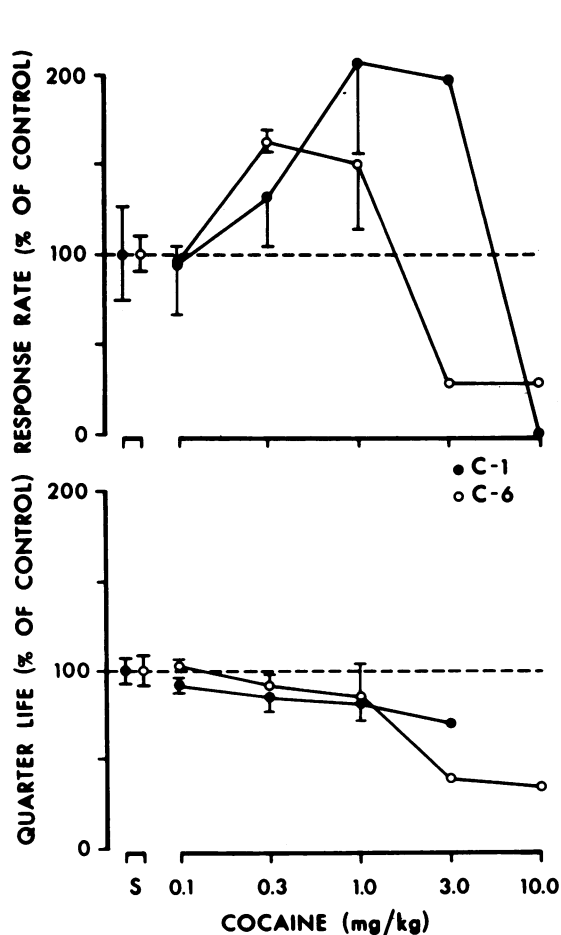


Fig. 1. Effect of cocaine on mean rate of responding (top) and mean quarter-life value (bottom) during a 10-min FI schedule of food delivery in chimpanzees C-1 and C-6. Doses of .1 to 1.0 mg/kg were administered twice; 3.0 and 10.0 mg/kg were each administered once. The horizontal broken line at 100% represents the mean response rate during five sessions when saline was injected (control). Vertical lines through the symbols indicate ± 1.0 standard deviation. Chimpanzee C-1 made no FI responses at 10.0 mg/kg; consequently, quarter life could not be plotted for this dose.

pattern of responding under the FI schedule was also affected by increasing doses of cocaine. The chimpanzees began responding earlier in the 10-min interval, and higher response rates typically persisted for the duration of the interval following cocaine injection. Quarter life, a measure of the distribution of responses during the interval, decreased gradually as the dose increased (Figure 1, bottom). At 3.0 and 10.0 mg/kg, quarter life under the FI schedule was suppressed substantially in chimpanzee

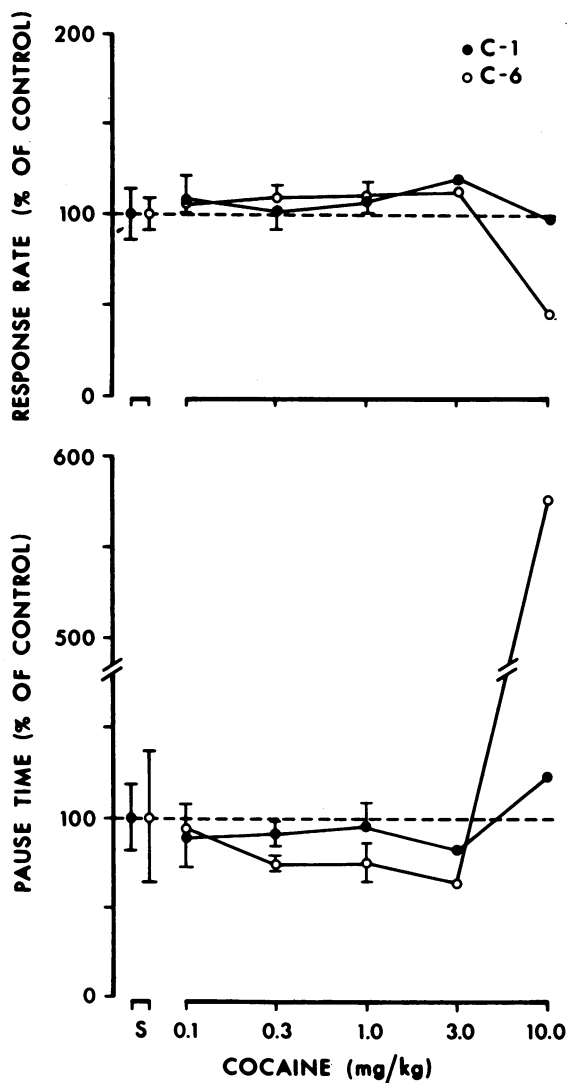


Fig. 2. Effect of cocaine on mean rate of responding (top) and mean pause time preceding the first response (bottom) during an FR 30 schedule of food presentation in chimpanzees C-1 and C-6. Other details as in Figure 1.

C-6, and chimpanzee C-1 made no response under the FI schedule at 10.0 mg/kg.

Figure 2 summarizes the effect of cocaine on responding under the FR schedule at doses of .1 to 10.0 mg/kg. In neither chimpanzee was there a systematic effect on rate or pattern of responding at doses below 10.0 mg/kg. At 10.0 mg/kg, however, the pause preceding the first response under the FR 30 schedule increased in duration, especially at the beginning of the session, and mean rate of responding decreased accordingly. The decrease in mean response rate (shown in Figure 2, top) was due primarily to the longer pause time at 10.0 mg/kg (Figure 2, bottom). Once responding began, the time required to execute 30 responses was comparable to that observed when saline was administered. The absolute FR values at each dose of cocaine are displayed in Table 1.

In contrast to the enhancement of responding under the FI schedule and the absence of an effect of cocaine on responding under the FR schedule at doses below 10.0 mg/kg, the drug decreased drinking in a dose-dependent manner (Figure 3). Total drinking was affected little at .1 to .3 mg/kg, but drinking was suppressed at higher doses. At 10.0 mg/kg, chimpanzee C-1 drank no water during the session, in contrast to an average of 2218 ml during nondrug sessions, and chimpanzee C-6 drank only 40 ml in contrast to a nondrug average of 410 ml. Figure 4 shows the distribution of drinking during the components of the mul-

tipale schedule for each chimpanzee and the effect of cocaine on drinking as dose increased. As can be seen, there was no evidence that the drug selectively altered drinking during specific components of the multiple schedule in either subject. The first half of the 10-min FI was the period of maximum water intake during nondrug sessions and also during drug sessions in which drinking occurred. Cocaine decreased drinking in a relatively uniform, generalized manner.

Cocaine suppressed conditioned behavior and adjunctive behavior and produced grand mal type convulsive seizures at 10.0 mg/kg. Approximately 8 to 10 min after injection of

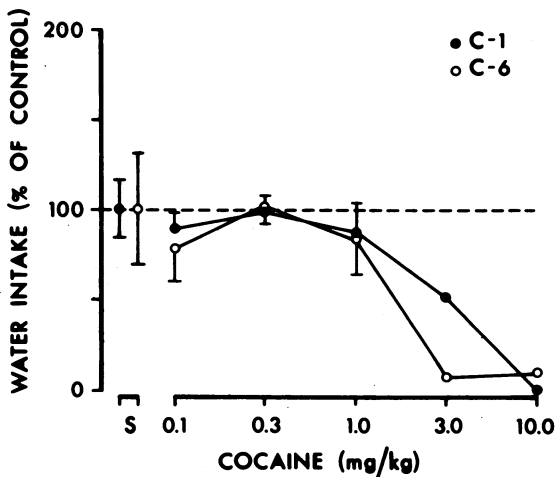


Fig. 3. Effect of cocaine on mean water intake during a 2-hr session in chimpanzees C-1 and C-6. Other details as in Figure 1.

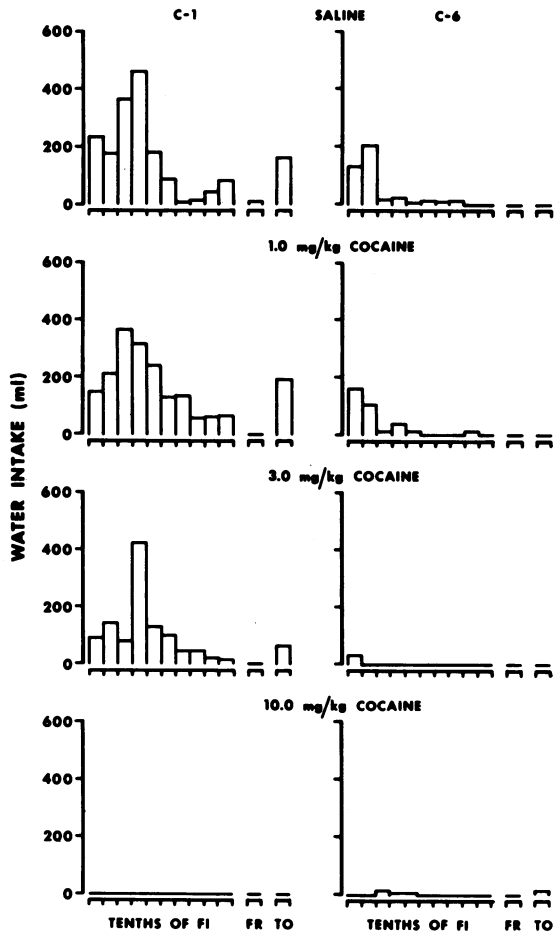


Fig. 4. Effect of cocaine on the distribution of drinking during successive 1-min segments (tenths) of a 10-min FI schedule, during an FR 30 schedule, and during 1-min timeout periods of a multiple schedule. The saline data are mean values based on five sessions when saline was injected. The data for 1.0 mg/kg are mean values from two administrations of this dose; 3.0 and 10.0 mg/kg were administered once.

this dose, each chimpanzee was observed lying on the bottom of the experimental chamber exhibiting pronounced muscular spasms. The seizures lasted 10 to 15 min, then the chimpanzee recovered and returned to its usual sitting posture for the remainder of the session. Responding under the FI schedule and adjunctive drinking were markedly suppressed for the duration of the session at 10.0 mg/kg, but responding under the FR schedule re-

covered and resembled control performance during most of the session.

Cumulative records showing control performance and the effects of the four highest doses of cocaine on patterns of conditioned and adjunctive behavior are shown in Figure 5. The records show the contrasting effects of cocaine on FI responding, FR responding, and adjunctive drinking at individual doses and reveal the basis of the increase in overall mean

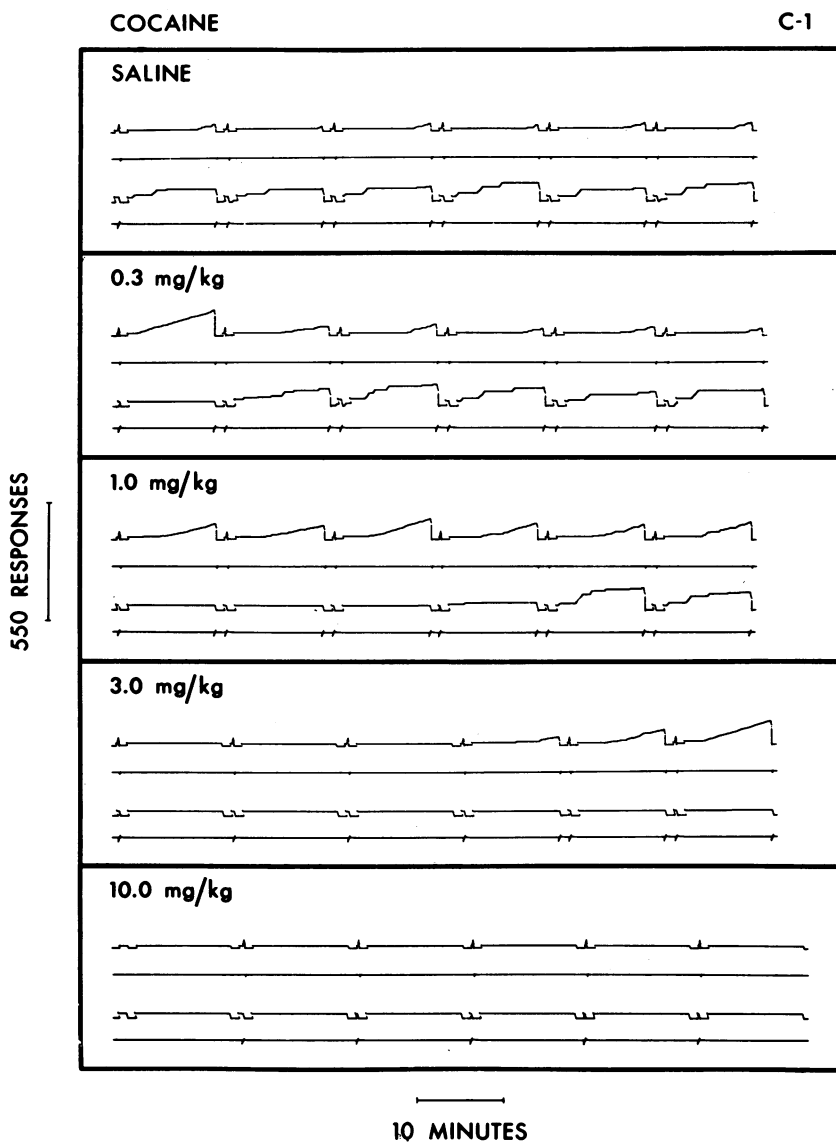


Fig. 5. Effect of cocaine on cumulative records of key pressing and drinking under *mult* FR 30 FI 10-min schedules of food presentation and 1-min timeout periods. Key-pressing responses are shown in the first pen tracing at each dose; drinking responses are shown in the third pen tracing. The second and fourth lines are event pen tracings, and vertical marks on them indicate food presentations. Downward displacement of the response pens indicates timeout. At each dose, records show the first six FR and FI components of the session.

response rates under the FI schedule displayed in Figure 1 (top). The increase in mean FI response rate at .3 mg/kg, for example, was due mainly to increases during the first few intervals of the session, whereas the increase in mean rate at 1.0 mg/kg was due to an enhancement of response rate extending over a larger portion of the session. The decreases in water intake shown in Figure 3 at various doses are shown in Figure 5 to be due also to differences in the duration of suppression of drinking as cocaine dose increased. At .3 mg/kg, the suppression of drinking was brief, and the duration of suppression increased with increases in cocaine dose.

Given the apparent dose-dependent differences in duration of effects evidenced by the cumulative records, a time-course analysis was performed based on response rate during each of the 9 successive FI 10-min schedules of the 2-hr session. Figure 6 shows the resulting response rates during successive FI components when either .3, 1.0, or 3.0 mg/kg was administered to chimpanzee C-1. The enhancing effect of .3 mg/kg cocaine was brief in duration and was restricted to the first FI component of the session. Response rates during the remaining FI components were similar to rates observed in the absence of cocaine. When 1.0 mg/kg was administered, the maximum increase in rate was greater, and it occurred several intervals later in the session, or approximately 50 min after injection. Moreover, response rate under the FI schedule remained at an elevated level during the remaining intervals in the session at 1.0 mg/kg. When 3.0 mg/kg was administered, responding was suppressed during the first several FI components; then responding resumed, increased to rates above control levels, and persisted at an elevated level for the rest of the session. The highest response rate at 3.0 mg/kg occurred during the second half of the session, more than 1 hr after the drug was injected. At 10.0 mg/kg, responding during the FI components was suppressed for an even longer period of time, and there was no indication of the recovery of responding during the FI components even at the end of the 2-hr session.

DISCUSSION

The present experiment shows that .1 mg/kg cocaine i.m. has little or no effect on con-

ditioned or adjunctive behavior in the chimpanzee, that higher doses can alter the rate and pattern of these behaviors, and that a dose of 10.0 mg/kg can produce a generalized grand mal type convulsive seizure. This range (.1 to 10.0 mg/kg) encompasses doses reported to alter conditioned responding maintained under FI and FR schedules in other nonhuman primates. Barrett (1976), Byrd (1979), Gonzalez and Goldberg (1977), and Spealman et al. (1977) found that .03 to .1 mg/kg cocaine had little effect on responding under FI schedules of food presentation, shock presentation, or shock termination in the squirrel monkey; that .3 to 1.0 mg/kg increased response rates, and that higher doses decreased rates. In the present experiment, cocaine had qualitatively similar effects on responding under FI schedules of food presentation in the chimpanzee. Moreover, the effects of cocaine on responding under FR schedules in the chimpanzee were qualitatively similar to the effects obtained in the squirrel monkey (Gonzalez & Goldberg, 1977; Spealman et al., 1977) and rhesus monkey (Johanson, 1978). Cocaine had no effect on FR responding at lower doses and decreased responding at high doses. Therefore, the present experiment extends the generality of the effects of cocaine on conditioned schedule-

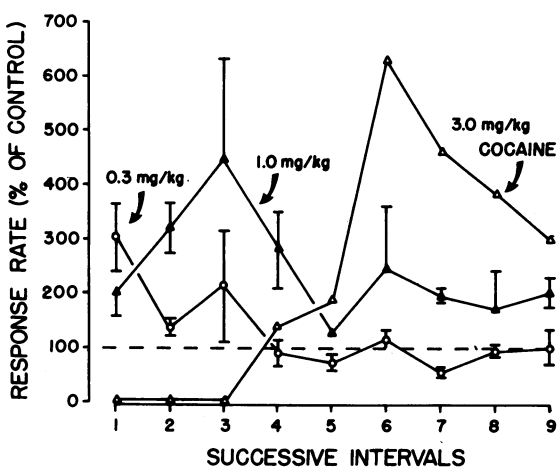


Fig. 6. Effect of cocaine on mean response rate during successive FI 10-min components of a 2-hr session in chimpanzee C-1. The horizontal broken line at 100% represents the mean rates obtained when saline was injected (control). Data are plotted as percentage change from the rates obtained during respective intervals on control days. Cocaine was administered i.m. approximately 20 min before the first 10-min interval.

controlled behavior in nonhuman primates to include a great ape species, the chimpanzee.

The effects of cocaine on adjunctive behaviors are less well documented and, consequently, less well understood. Moreover, most of the reports which are available describe the effects of cocaine on aggressive types of adjunctive behavior. Moore and Thompson (1978) studied cocaine in the pigeon and observed differential effects on conditioned and adjunctive behavior. They found that there were doses which decreased adjunctive pecking directed toward the pigeon's image in a mirror but did not affect key pecking that resulted in food presentation. Hutchinson, Emley, and Krasnegor (1977) studied the effects of cocaine in the pigeon under a similar procedure and obtained similar differential effects on food-reinforced and adjunctive pecking directed toward a stuffed pigeon. Hutchinson et al. also studied the effects of cocaine on hose biting in the squirrel monkey when the biting response resulted in food presentation and when the biting response postponed electric shock. Under these procedures, biting was a conditioned behavior, and cocaine increased the frequency of biting.

In the present experiment, key pressing was conditioned in the chimpanzee and maintained under *mult* FR FI schedules of food presentation; and drinking, a nonaggressive response, occurred adjunctively to key pressing, i.e., drinking was not explicitly reinforced or conditioned but it occurred consistently in concert with conditioned behavior. Although the total water intake per session did not deviate substantially from nondrug or control levels when cocaine doses as large as .3 or 1.0 mg/kg were administered, the cumulative records (Figure 5) revealed transient effects on adjunctive drinking at these doses. At .3 mg/kg, drinking was suppressed briefly at the beginning of the session, then returned to control levels during the rest of the session. On the basis of these data, cocaine acted differentially on conditioned behavior and adjunctive behavior since responding under the FI schedule increased at a dose of .3 mg/kg. Moreover, the data in Figure 2 showed that conditioned responding under the FR schedule was not affected at doses of .1 to 3.0 mg/kg, yet drinking decreased and FI responding increased at most of these doses. Comparing adjunctive drinking with conditioned key pressing under the FR

schedule would also lead to the conclusion of differential effects of cocaine. Thus, the findings suggest that cocaine can differentially affect behavior in the chimpanzee as a function of the type of behavior, differences in procedures under which the behavior is engendered and maintained, or both. Differences in control rates cannot easily be invoked to explain the differential effects since FI rates of key pressing were higher than rates of drinking under the FI schedules for chimpanzee C-6 but lower for chimpanzee C-1, yet cocaine had similar effects in the two subjects. At a given dose, key pressing under the FI schedule increased and drinking under the FI schedule decreased.

Cocaine has traditionally been characterized as a local anesthetic and psychomotor stimulant (Ritchie & Cohen, 1975); however, there is substantial evidence that the drug is also a potent convulsant (Eidelberg, Lesse, & Gault, 1963; Stevens, Mark, Erwin, Pacheco, & Sue-matsu, 1969). Doses of 4.0 to 8.0 mg/kg administered intravenously can produce clonic convulsions with epileptiform seizures in the rhesus monkey (Matsuzaki, 1976) and, in the present study, 10.0 mg/kg administered intramuscularly produced similar convulsions and seizures in the chimpanzee. In the rhesus monkey, the convulsions were approximately 1.0 min in duration at 4.0 to 5.0 mg/kg and increased to approximately 3.0 min at 8.0 mg/kg. In the chimpanzee, convulsions lasting 10 to 15 min were observed following a dose of 10.0 mg/kg. These data suggest that cocaine has similar convulsant effects in different species independently of route of administration and that the duration of convulsions is dose related.

The time-course analysis revealed the relation between duration of effect and dose of cocaine in the chimpanzee and the extent to which a single summary measure derived from a relatively lengthy observational period or experimental session can be misleading. The effect of .3 mg/kg in suppressing drinking and enhancing key pressing was limited primarily to the first half-hour following drug administration (Figures 5 and 6), yet this was not conveyed in the dose-effect curves presented in Figures 1 and 3. Moreover, the overall mean rates in Figure 1 suggested little difference in the effects of 1.0 and 3.0 mg/kg on FI responding in chimpanzee C-1, but Fig-

ures 5 and 6 revealed considerable difference. At 1.0 mg/kg, there was enhancement of responding under the FI schedule throughout the session. At 3.0 mg/kg, however, a variety of behavioral effects was observed including an initial period of complete suppression followed by a period of recovery, then maximum enhancement of responding, then a period of lesser enhancement, and finally a return toward baseline rates. These data indicate the need for caution in characterizing behavioral performance via a single summary measure, especially where relatively short-acting drugs are involved. The time course of the behavioral effects in the chimpanzee was similar to the time-course effects of cocaine in the squirrel monkey (Gonzalez & Goldberg, 1977; Reints, 1979; Spelman et al., 1977) and in the rat (MacPhail & Seiden, 1975). Recent experiments have also shown that the effect of cocaine on systemic arterial blood pressure in the squirrel monkey (Gonzalez & Byrd, 1977; Reints, 1979) and in humans (Fischman et al., 1976) is comparably brief.

Gonzalez and Goldberg (1977, p. 43) have commented on the value of time-course data in clarifying summary measures describing the effects of cocaine, and MacPhail and Seiden (1975) have emphasized the significance of posttreatment time as a determinant of the behavioral effects of the drug. The results of the present experiment call attention to the importance of the type of behavior under study, the procedures under which the behavior is engendered and maintained, and the duration of effect when describing the ways in which drugs and behavior interact. Moreover, the results suggest that, whereas the effects of cocaine on adjunctive behavior contrast with those on conditioned behavior, the effects of cocaine on aggressive adjunctive behavior (data reported by Moore & Thompson, 1978, and Hutchinson et al., 1977) and nonaggressive adjunctive behavior (the present data) are similar.

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